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ORIGINAL ARTICLE

Seroepidemiology of a second epidemic of hepatitis E in a population that had recorded first epidemic 30 years before and has been under surveillance since then

Mehnaaz Sultan Khuroo · Mohammad Sultan Khuroo

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Abstract
Purpose Large-scale waterborne epidemics of hepatitis E occur in developing countries. It is not known why these epidemics occur repeatedly and selectively in adult population?
Methods We studied seroepidemiology of an outbreak of hepatitis E in one of 15 villages that had recorded first epidemic of hepatitis E 30 years back. Another village not affected by the second epidemic was taken as a control. Overall, 1,216 sera were collected (638 from the epidemic village and 578 from the control village) for serological markers of both hepatitis A virus (HAV) and hepatitis E virus (HEV).
Results The seroprevalence of anti-HEV in this population following the first epidemic in 1978 was 29.4%. Antibodies were detected in only 47% of the 45 patients affected by icteric HEV infection 14 years after the first epidemic. At 30-year follow-up, the seroprevalence of anti-HEV was only 4.5% (26/578). In the village affected by second epidemic, 138 (21.6%) subjects had serological evidence of recent HEV infection. The attack rate was 23.6% (78/330) in children (≤14 years) and 19.4% (60/308) in adults ($P = 0.21$). The attack rate of anicteric HEV infection was 21.8% (72/330) in children and 14.6% (45/308) in adults ($P = 0.02$).
Conclusions Following hepatitis E epidemics, there is a gradual loss of antibodies in the community over the decades and poor exposure to HEV infection in the cohort of population born during the interepidemic period. The next epidemic occurs when antibody levels fall to critically low levels and there is associated gross fecal contamination of water resources. During epidemic, persons of all age groups are exposed to infection, with predominant anicteric disease in children.

Keywords Hepatitis E virus · Hepatitis A virus · Epidemic · Epidemiology · Kashmir · Anti-HEV

Mehnaaz Sultan Khuroo
Department of Pathology, Sher-i-Kashmir Institute of Medical Sciences, Soura 190 001, Kashmir, India
e-mail: mkhuroo@yahoo.com

Mohammad Sultan Khuroo (✉)
Digestive Disease Centre, Dr. Khuroo's Medical Clinic, Srinagar 190 001, Kashmir, India
e-mail: khuroo@yahoo.com

Introduction

Hepatitis E was first recognized during an epidemic of hepatitis, which occurred in Kashmir in 1978 [1]. Very soon, hepatitis E was retrospectively traced to an epidemic of acute viral hepatitis, which had occurred in Delhi, India, in 1955–1956 [2]. The infection was successfully transmitted into an individual in 1983 by self-ingestion of acute-phase stool suspensions from waterborne epidemic of non-A hepatitis in Central Asia [3]. Hepatitis E virus (HEV) was cloned and sequenced in 1990 [4].

Hepatitis E is an emerging infectious disease [5]. The disease is caused by a well-characterized virus, the hepatitis E virus. HEV is a small, round, nonenveloped particle of 27–34 nm, with a genome of approximately 7.2 kb in length that consists of a polyadenylated, single-stranded RNA molecule containing three discontinuous and partially overlapping, open-reading frames (ORFs) and 5′ and 3′ *cis*-acting elements that have important role to play in HEV replication and transcription. HEV is the sole member of the genus Hepevirus in the family of Hepeviridae.

Hepatitis E is a major public health problem in developing countries [6]. It causes large-scale waterborne epidemics of acute hepatitis and sporadic infections in developing countries. Data from serosurveys have forced a reevaluation of the epidemiology and distribution of the virus, with the result that the virus is global in distribution with autochthonous infections in developed countries, originating from foodborne zoonotic transmission [7].

The epidemiology of hepatitis E has many enigmatic characteristics. Increased incidence and severity of HEV infection in pregnancy have remained unexplained [8–10]. Recent data have pointed to the relationship between severity of HEV infection in the mother and vertically transmitted HEV infection in the fetus [11]. Another epidemiological feature of HEV infection that has remained unanswered is the occurrence of disease in adult population [1]. The reason for this pattern of age distribution for an enteric infection is unusual. Occurrence of repeated attacks of large-scale epidemics of jaundice in endemic areas is another unanswered puzzle [12]. We had a unique opportunity to study a second attack of HEV outbreak in a population that recorded the first HEV epidemic 30 years earlier [1], and we believe observations from this epidemic might help answer some of these questions about epidemiology of HEV infection in endemic areas.

Materials and methods

In November 2007, an outbreak of jaundice was reported in Maharajpora village by the block medical officer of subdistrict hospital of Sopore to Director Health Services, Kashmir. We established a medical camp in the area within 2 weeks of the first report to study this outbreak of hepatitis.

Maharajpora village is located in Sopore town, district Baramulla, Kashmir, India, and has a total population of 720 individuals (based on census done by us in 2007). District of Baramulla (population 1,700,000 in 1978) recorded large-scale epidemics of hepatitis in 1978–1982 [1, 12–14]. There were estimated 52,000 cases of icteric hepatitis, more than 2,000 cases of fulminant hepatitis and 1,750 deaths. To study the first epidemic in 1978–1979, we had chosen an area of 15 villages with a population of 16,620 (11 epidemic villages and 5 control villages) for intense house-to-house study and since then it has been under our constant surveillance [1]. Maharajpora is among one of these 15 villages. On the basis of survey of these 15 villages and serologic tests for hepatitis A and hepatitis B, we reported this epidemic as of non-A, non-B type and indicated to the possibility of another human hepatitis virus distinct from posttransfusion non-A, non-B type. Over a 6-week period from November 1978 to January 1979, 269 (2.1%) cases of icteric hepatitis E were recorded in 11 epidemic villages (population 12,900). In addition, 35 (27.3%) of the 128 apparently healthy subjects had elevated levels of liver enzymes (anicteric hepatitis) and were later found to be reactive for IgG anti-HEV (anicteric HEV infection). Thus, the overall attack rate of epidemic HEV infection in these 11 villages was 29.4%. Increased incidence and severity of epidemic hepatitis in pregnancy were reported on the basis of the same survey [8]. We conducted another census and survey of this region 18 months after the first epidemic to assess whether disease was self-limiting or not [15]. In 1992, we studied this region for the long-term HEV-antibody status of patients who had documented HEV in 1978 [16]. IgG anti-HEV was detected in 21 (47%) of the 45 patients who had icteric HEV infection in 1978. This suggested that IgG anti-HEV was lost in more than half of patients over the 14-year period.

In 1978, population of this region was using drinking water from a local stream (Ningli Nallah) flowing through the region. Residents would collect water for use from open stream in earthen containers. Unfortunately, these open waterways were also used for sewage disposal of this region, leading to gross fecal contamination. Following these unprecedented epidemics, along with its political impact and socioeconomic developments, government envisaged a large project to supply piped and chlorinated water to this region. During these 30 years, no outbreak or epidemic of jaundice was reported from this region. Recently, these water sources have come under pressure to supply adequate drinking water to this region. In August 2007, an alternate water supply scheme was opened up for Maharajpora village. This scheme provided piped water from Jhelum River. The point from where water was collected was 300 m downstream from the point where all the sewage of the region was disposed in the river. In addition, the treatment (chlorination) plant of the water supply scheme was not installed for first 3 months, allowing supply of raw river water to the residents. This led to the supply of grossly contaminated drinking water to Maharajpora.

For the present study, we selected Maharajpora village (study population) and Batpora village (population 608, control population). Batpora village, one of 11 affected villages of 1978 epidemic under our surveillance, is situated 2 km from Maharajpora, had supply of piped chlorinated water, and had recorded no outbreak or epidemic of jaundice since 1978. A house-to-house survey of both villages was done for cases of jaundice, and all residents were requested for a blood sample for biochemical and serologic studies. All sera were tested for serum bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), as well as serological makers for hepatitis viruses. Serology for hepatitis viruses was performed by enzyme immunosorbent assay (ELISA) for markers of hepatitis A virus (HAV) (IgG and IgM anti-HAV), HBV

(HBsAg and IgM anti-HBc), and HCV (anti-HCV second generation) using commercially available kits from Abbott Laboratories (North Chicago, IL, USA). Sera from all patients were also tested by ELISA for IgG and IgM antibodies to HEV by a kit using recombinant HEV antigens corresponding to ORF2 of the HEV (Diagnostic Biotechnology, Singapore). The assays were performed strictly according to manufacturer's instructions.

The criteria for the diagnosis of icteric viral hepatitis were as follows: (1) recent onset of jaundice in the absence of history of jaundice or chronic liver disease; (2) no other cause to account for jaundice; (3) serum bilirubin level of 2.0 mg/dL or more, with an increase in transaminases 2.5 times above the upper limit of normal (AST 0–38 U/L and ALT 5–41 U/L). Anicteric hepatitis was diagnosed in subjects who had elevated levels of liver enzymes with serum bilirubin levels of less than 2 mg/dL.

Diagnosis of hepatitis E infection was made when sera were reactive to IgM anti-HEV and/or IgG anti-HEV in patients with elevated levels of liver enzymes. Diagnosis of acute hepatitis E on the basis of IgG anti-HEV positivity in a patient with elevated levels of liver enzymes was accepted in this unique epidemic setting because seropositivity of anti-HEV in the same population (control village) was very low (4.5%) and negligible in patients of early age groups. Subjects with reactive IgG anti-HEV alone with normal liver function tests were considered to have previous exposure to HEV infection. Diagnosis of HAV infection was made when sera were reactive to IgM anti-HAV. Subjects with reactive IgG anti-HAV alone were considered to have previous exposure to HAV infection.

Statistical methods

Comparisons of categorical variables were analyzed using either Fisher's exact test when any of the expected value was less than 5 or chi-square test for all others. Comparisons of continuous variables were analyzed using Student's *t* test for normally distributed variables and Mann–Whitney *U* test for non-normally distributed variables. Variables with skewed deviation (serum bilirubin and ALT) were normalized using log transformation for analysis. Odds ratios (ORs) were computed from the coefficients and their 95% confidence intervals (CIs) were calculated. All values are expressed as mean ± 1 SD. *P* value of <0.05 was considered significant.

Results

Outbreak

During the 3-month period (November 2007–January 2008), 21 (13 men and 8 women; age 23.0 ± 5.3 years) patients suffered from icteric hepatitis. Two patients (1 third-trimester pregnant woman and one 65-year-old man) developed fulminant hepatic failure and died. All patients resided in Maharajpora, and no case of icteric hepatitis was reported from Batpora. None of the 21 patients with icteric hepatitis had hepatitis E infection in 1978–1979 epidemic, and none of these had developed icteric hepatitis as shown in the follow-up records from the surveillance data. All 21 sera were reactive to IgM anti-HEV and were negative for acute markers of hepatitis A (IgM anti-HAV), hepatitis B (HBsAg and IgM anti-HBc), and hepatitis C (anti-HCV).

Sera collection

A total of 1,216 (91.6%) sera samples were collected. This included 638 (88.6%) sera from the epidemic area and 578 (95.1%) from the control area.

HAV epidemiology

Of the 1,216 sera tested, 1,004 (82.5%) were IgG anti-HAV reactive. The seroprevalence of IgG anti-HAV in the epidemic area (522/638; 81.8%) and the control area (482/578; 83.4%) did not differ significantly ($P = 0.45$). Age-wise seroprevalence showed early saturation suggestive of HAV infection in early years of life (Table 1). Thirty-nine sera were reactive for IgM anti-HAV. All acute hepatitis A infections occurred in children between 3 and 10 years of age and all had anicteric disease. HAV infection was detected in 21 (21/638; 3.3%) children in the epidemic area and in 18 (18/578; 3.1%) children in the control area ($P = 0.87$). Seroepidemiology of HAV in 1978 had been studied and at that time, 197 (96.1%) of the 205 sera were positive for IgG anti-HAV [1].

HEV epidemiology in control area

Twenty-six (4.5%) of the 578 sera were reactive for IgG anti-HEV. The seroprevalence of IgG anti-HEV was 0.8% (1/120) in age group up to 10 years, 0.7% (1/130) in age

Table 1 Decade-wise seroprevalence of antibodies to hepatitis A virus (IgG and IgM type) in 1,216 sera collected from two villages

Age group (years)	Sera tested	IgG anti-HAV (%)	IgM anti-HEV (%)
<10	374	247 (66.0)	39 (10.4)
11–20	250	212 (84.8)	0
21–30	236	212 (89.8)	0
31–40	198	183 (92.4)	0
>40	158	150 (94.9)	0
Total	1,216	1,004 (82.6)	39 (3.2)

group 11–20 years, 3.5% (4/116) in age group 21–30 years, 9.3% (10/108) in age group 31–40 years, and 9.6% (10/104) in age group more than 40 years. Four subjects were reactive for IgM anti-HEV. All four subjects with HEV infection had anicteric hepatitis and abnormal liver enzymes normalized in the follow-up.

HEV epidemiology in epidemic area

Twenty-one (13 men and 8 women; age 23.0 ± 5.3 years) patients had icteric hepatitis. In addition, 117 subjects had elevated levels of liver enzymes with normal serum bilirubin levels (anicteric hepatitis). Of these 138 subjects (icteric and anicteric hepatitis), 64 sera were reactive for IgM anti-HEV and IgG anti-HEV and remaining 74 subjects were reactive for IgG anti-HEV alone. The overall attack rate of HEV infection was 21.6%. The attack rate was 23.6% (78/330) in children (≤14 years) and 19.4% (60/308) in adults ($P = 0.21$; OR = 1.27, 95% CI = 0.86–1.80). The attack rate of icteric HEV infection was 1.8% (6/330) in children and 4.9% (15/308) in adults ($P = 0.03$; OR = 2.7, 95% CI = 1.06–7.02). The attack rate of anicteric HEV infection was 21.8% (72/330) in children and 14.6% (45/308) in adults ($P = 0.02$; OR = 1.63, 95% CI = 1.1–2.36). Icteric to anicteric HEV infection ratio in children was 1:12.1. In contrast, icteric to anicteric ratio of HEV infection in adults was 1:2.9 ($P = 0.005$) (Table 2).

Another 18 subjects were reactive for IgG anti-HEV alone with normal liver function tests and were considered to have previous exposure to HEV.

Discussion

Large-scale waterborne epidemics of HEV have occurred in many tropical and subtropical countries in which thousands of individuals developed acute hepatitis following ingestion of contaminated water [1, 2, 5–7]. From 1985 to 2004, ten major epidemics of HEV have been recorded involving 327,280 reported human cases in the Indian subcontinent and Southeast and Central Asia [6]. This is the tip of the iceberg because many epidemics that occur are not studied and published. Other countries that experienced epidemics of HEV include African countries of Algeria, Chad, Ethiopia, Ghana, Ivory Coast, Namibia, and Sudan and the Asian countries of Burma, China, Myanmar, Nepal, Pakistan, and Vietnam. In fact, refugee camps of Africa have become a preferred target for major HEV epidemics. All these epidemics have few common features, which include compressed epidemic curve, large-scale population involvement, occurrence of disease in adult population, high incidence and severity of disease in pregnant women, and major morbidity and mortality in affected population. HEV epidemics are a major public health problem in developing countries and will remain so until the water supplies and sanitation of these regions are improved to optimum.

Several characteristics of HEV epidemics in developing countries are unexplained. Repeated occurrences of these epidemics and selective occurrence of disease in adults are puzzling because the disease is transmitted by the fecal-oral route via contaminated water [12]. HAV, which is transmitted through fecal-oral route, selectively infects children in these countries, and majority of the population is exposed to HAV in first few years of life. Antibody response to HAV is robust and long-lasting, and HAV infection in adults is rare. Epidemics of HAV infections in adults in developing countries do not occur. Several questions need to be answered to explain this diverging epidemiology of these two agents. First, why disease is selective in adults? Does HEV infection run an anicteric course in children followed by a gradual loss of immunity, or does HEV somehow has a selective tropism for liver cells of adults? Second, how repeated epidemics of disease occur in these communities? Following such large-scale epidemics, should population have antibodies to protect from another epidemic? This again leads to question whether antibodies are protective and long-lasting.

Table 2 Attack rate of hepatitis E infection (overall), icteric and anicteric hepatitis E infection, their ratio in children and adults during 2007–2008 epidemic

	Age group, number tested (%)			Children vs. Adults	
	Total ($N = 638$)	Children (≤14 years, $N = 330$)	Adults (>14 years, $N = 308$)	P	OR (95% CI)
HEV infection				0.21	1.27 (0.86–1.80)
Icteric HEV	21 (3.3)	6 (1.8)	15 (4.9)	0.03	2.76 (1.06–7.02)
Anicteric HEV	138 (21.6)	78 (23.6)	60 (19.5)	0.02	1.63 (1.1–2.36)
Icteric:anicteric ratio	1:5.6	1:12.0	1:3.0	0.005	–

The data show that attack rate of overall hepatitis E infection in children and adults did not differ. Adults more often presented with icteric disease, whereas children more often had anicteric infections

Although numerous epidemics of HEV have been studied, there has never been an opportunity to study the second epidemic of HEV infection in the same population.

We had a unique opportunity to examine some issues related to the epidemiology of hepatitis E. A well-documented epidemic of HEV occurred in Baramulla district of Kashmir in 1978 [1]. We had done extensive house-to-house survey of 15 villages, with a population of 16,620, in November 1978–January 1979. During this epidemic, we have data on the seroprevalence of IgG anti-HEV following this epidemic. Since then, this region has been under constant surveillance for disease occurrence and has not recorded another epidemic or outbreak till 2007. We studied this population 14 years after the first epidemic to define the seroprevalence of IgG anti-HEV. In 2007, the second outbreak of HEV occurred in one of these 15 villages, and we had the opportunity to study contrasting seroprevalence of HEV infection in the affected village (second epidemic) and the control village (30 years after the first epidemic). Several facts have emerged from these data.

Following the first epidemic of 1978–1979, more than one-fourth (29.4%) of the population had been exposed to HEV infection and was reactive to IgG anti-HEV. There was a gradual loss of IgG anti-HEV over the next 14 years, and when sera from 47 documented HEV cases were tested, only less than half (47%) of these subjects had persistent IgG anti-HEV. We studied seroprevalence of IgG anti-HEV in the control village 30 years after the first epidemic and found only 4.5% of the population had antibodies to HEV. Of interest is the observation that only two of 250 subjects younger than 20 years in the control village were seropositive for IgG anti-HEV. The seroprevalence of IgG anti-HEV was 3.5% in the third decade and around 10% in the fourth decade onward. These findings suggested that the new cohort of population (those born following the epidemic) had little exposure to HEV infection during 30 years following the epidemic, possibly through occasional sporadic infections. Second, those exposed to HEV in 1978 had a gradual loss of antibodies from 29.4 to 7.3% (24/328; subjects older than 30 years) over the next three decades. We believe that a gradual loss of antibodies in the population exposed to HEV epidemic and a lack of substantial exposure to HEV infection during the interepidemic period are crucial to repeated occurrences of the epidemics in developing countries. The next epidemic in a population occurs when a substantial population is seronegative for antibodies (a combination of new cohort born after the last epidemic and a gradual loss of antibodies in those previously infected) and environmental conditions are right for large-scale water pollution. The issue why substantial exposure to HEV does not occur during interepidemic period as in HAV may be related to contrasting pathogenicity of these two viruses. HAV is a highly pathogenic virus and can spread by contact transmission as well as through food and water. In contrast, HEV is less pathogenic, does not spread by contact transmission, and needs gross fecal contamination of water resources to cause disease.

We studied the age-related attack rate of icteric and anicteric HEV during the outbreak in the epidemic village. The overall attack rate of HEV infection in children and adults did not differ from each other. However, the proportion of children with anicteric disease was higher than in adults. Thus, children are not immune to HEV infection and get HEV infection as common as adults. More recently, a second general pattern of anti-HEV seroprevalence has been recognized [17]. In Egypt, the anti-HEV pattern more closely follows the anti-HEV pattern observed in India; antibody to HEV is common in children and seroprevalence plateaus at levels of 70% or higher starting in young children. Large-scale epidemics of HEV do not occur in Egypt, although sporadic cases of hepatitis E are diagnosed.

We compared the seroepidemiology of HAV over a 30-year period from 1978 to 2007. In 1978, 197 (97.1%) of 205 sera were positive for IgG anti-HAV [1]. The seroprevalence of IgG anti-HAV in 2007 was 82.5% (1,004/1,216). Age-specific seroprevalence of IgG anti-HAV showed early saturation, suggesting exposure to HAV infection in the first few years of life. In fact, subclinical acute HAV infection was seen in 39 children in the age group 2–10 years.

All studies have shown a relatively low seroprevalence of IgG anti-HEV in general population in the Indian subcontinent. However, within these reports, there is a wide range of IgG anti-HEV positivity from 4 to 30%. Antibody to HEV is infrequent in children, increases mainly during young adulthood and plateaus at moderately low levels in less than 40% of adults [18]. Data from the present study give a clue of this pattern of anti-HEV seroprevalence. We believe seropositivity is a function of the time gap between the last epidemic of HEV in the region and the study time. If antibody seroprevalence study is done within the first few years of a previously recorded epidemic, seropositivity of IgG anti-HEV may reach as high as 30%. However, if epidemic in the region had occurred few decades ago, the seroprevalence of anti-HEV would be correspondingly low. Low percentage of seroprevalence of anti-HEV in children and young adults is related to low exposure to HEV in this new cohort (born after the epidemic) during interepidemic periods.

On the basis of these observations, we have developed a model of how repeated epidemics of hepatitis E occur in the Indian subcontinent. Data show that hepatitis E epidemic occurs when antibody levels in the population are

low and there is gross fecal contamination of water resources. Once an epidemic breaks out, one-fourth to one-third (25–30%) of the population is exposed to infection. All age groups are uniformly exposed to infection. Icteric disease occurs in about 2–3% of population. As disease in children is predominantly anicteric, icteric HEV predominantly occurs in adult population. Following the epidemic, there is a gradual loss of antibodies to HEV in the community. The prevalence of antibodies falls by half in 15 years and to one-quarter by three decades. Thus, population in the fourth decade and more is expected to have the seroprevalence of IgG anti-HEV of about 5–7%. The subjects born after the epidemic (first three decades) show negligible exposure to HEV and have very low seroprevalence of antibody to HEV. Thus, after three decades, the stage is set for a new epidemic and as soon as there is gross fecal contamination of water resources, an epidemic repeats itself.

These data may have important implication for vaccine control strategy for HEV disease in endemic areas. HEV vaccine has passed through phase 2 studies in Nepal, and on short-term follow-up has shown to be efficacious and safe [19]. However, it is not known how long the antibodies persist after vaccination [20]. Following natural infection, antibodies show a gradual loss over decades and if it is so after vaccination, it may control epidemics and sporadic infections for extended period of time. A booster dose of vaccine may be needed, and the time for its administration can be determined only from long-term follow-up studies.

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